Risk of Ectopic Pregnancy and Previous Induced Abortion

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ABSTRACT

Objectives. This study investigated the role of prior history of induced abortion in subsequent ectopic pregnancies.

Methods. Data from two French case–control studies were used to examine the effect of induced abortion on ectopic pregnancy risk. Case patients (n = 570) were women admitted for ectopic pregnancy during the study period; controls (n = 1385) were women who delivered in the same center.

Results. The analysis among women with no previous ectopic pregnancy showed that, after control for the main ectopic pregnancy risk factors, prior induced abortion was associated with an increased risk of ectopic pregnancy (odds ratio [OR] = 1.5, 95% confidence interval [CI] = 1.0, 2.0); there was a significant trend between number of previous induced abortions and ectopic pregnancy risk (ORs = 1.4 for 1 previous induced abortion and 1.9 for 2 or more).

Conclusions. This study suggests that induced abortion may be a risk factor for ectopic pregnancy for women with no previous ectopic pregnancy, particularly in the case of women who have had several induced abortions. (*Am J Public Health.* 1998;88:401–405)

Introduction

During the past 20 years, there has been a threefold to fourfold rise in the incidence of ectopic pregnancy in developed countries,[1,2] and ectopic pregnancies presently constitute about 1.5% of all reported pregnancies.[3–5] Despite progress in terms of diagnosis and treatment, ectopic pregnancy is still the leading cause of maternal death during the first trimester of pregnancy.[1] Also, ectopic pregnancy causes serious reductions in subsequent fertility, with a 20% chance of recurrence and a 20% to 40% chance of definitive infertility.[3] Several ectopic pregnancy risk factors have been identified, including pelvic inflammatory disease, smoking at the time of conception, pelvic surgery, previous use of an intrauterine device, and induced ovulation.[3,6–8] Current use of an intrauterine device is also associated with ectopic pregnancy, because it lowers the risk of uterine pregnancy more than the risk of ectopic pregnancy.[3] In a French study, these factors, in combination, explained approximately 65% of all ectopic pregnancies,[9] suggesting that about one third of ectopic pregnancies occur in women with no identified risk factors. In the framework of research on other risk factors, we investigated the role of previous reproductive outcomes (previous ectopic pregnancy and pervious spontaneous and induced abortions) in terms of the risk of subsequent ectopic pregnancy. Here we present results concerning the role of prior induced abortion, which remains debated.

Studies on the issue have provided discordant conclusions. Most of the oldest studies showed a strong association between the 2 events.[10] However, these studies were conducted in countries where induced abortion was still illegal, so their conclusions cannot be generalized because of underreporting or high occurrence of infectious complications, which could be the direct cause of subsequent ectopic pregnancy. The majority of the more recent studies (mostly performed in the United States)[11–15] have not revealed any significant association, but they generally have not included enough subjects to allow satisfactory statistical power. Thus, their nonsignificant results do not provide strong evidence of the absence of such a link.

Using data from 2 case–control studies, we investigated a large sample to ascertain whether induced abortion was associated with an increased risk of subsequent ectopic pregnancy in France, where induced abortion has been legal since 1975.

Methods

Subjects

Our sample was composed of subjects from 2 case–control studies on risk factors for ectopic pregnancy conducted in the same way in 2 French regions. The first study took place in 7 Paris-area maternity centers in 1988;[6] the second study was conducted in the Rhône–Alps area in 15 maternity centers between 1989 and 1991.[16] The participating centers cared for pregnant women living in the same area.

Case patients were all women younger than 45 years of age who were admitted for

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TABLE 1—Socioeconomic and Medical History Variables: Case Patients and Controls

	Case Patients[a] (n = 570), No.	(%)	Controls[a] (n = 1385), No.	(%)	Odds Ratio[b]	(95% Confidence Interval)
Age, y						
≤24	85	(15.0)	301	(21.9)	1.0	. . .
25–29	198	(34.8)	618	(45.0)	1.1	(0.8, 1.5)
30–34	175	(30.8)	312	(22.7)	2.0	(1.4, 2.7)
35–39	84	(14.8)	117	(8.5)	2.5	(1.7, 3.6)
≥40	26	(4.6)	25	(1.8)	3.4	(1.8, 6.4)
Education						
None	15	(2.6)	34	(2.5)	1.0	. . .
Primary	109	(19.1)	283	(20.5)	1.1	(0.5, 2.1)
Secondary	300	(52.7)	737	(53.3)	1.1	(0.6, 2.1)
Higher	146	(25.6)	328	(23.7)	1.2	(0.6, 2.3)
Current smoking						
No	314	(55.5)	955	(69.0)	1.0	. . .
Yes	252	(44.5)	428	(31.0)	1.8	(1.5, 2.3)
Previous pregnancies						
None	150	(26.3)	424	(30.6)	1.0	. . .
1	146	(25.6)	419	(30.2)	1.0	(0.8, 1.3)
2	132	(23.2)	289	(20.9)	1.3	(1.0, 1.7)
3 or more	142	(24.9)	253	(18.3)	1.5	(1.2, 2.2)
Prior genital infections						
None	179	(32.3)	816	(62.0)	1.0	. . .
Lower genital tract	108	(19.5)	318	(24.2)	1.5	(1.1, 2.0)
PID or *C trachomatis* seropositivity	267	(48.2)	182	(13.8)	6.4	(5.0, 8.3)
Prior ectopic pregnancy						
No	471	(82.6)	1362	(98.3)	1.0	. . .
Yes	99	(17.4)	23	(1.7)	10.3	(6.4, 16.7)
Prior pelvic surgery						
No	422	(74.0)	1312	(94.7)	1.0	. . .
Yes	148	(26.0)	73	(5.3)	5.8	(4.2, 8.1)
Induced conception cycle						
No	518	(90.9)	1351	(97.5)	1.0	. . .
Yes	52	(9.9)	34	(2.5)	3.6	(2.3, 5.8)
Previous use of contraception						
No	94	(16.5)	157	(11.3)	1.0	. . .
Intrauterine device	84	(14.7)	136	(9.8)	1.2	(0.8, 1.7)
Other	392	(68.8)	1092	(78.9)	0.7	(0.5, 0.9)

Note. PID = pelvic inflammatory disease.
[a]Figures may vary for some variables as a result of missing values.
[b]Adjusted for maternity center.

ectopic pregnancy during the study period and whose diagnosis was confirmed by laparotomy or laparoscopy (279 women in the Paris area and 624 in the Rhône–Alps area). Controls were women younger than 45 years of age admitted for delivery in the same center immediately after the corresponding case patient. For each case patient, 1 control was included in Paris and 2 in the Rhône–Alps area (except for 1 case patient for whom only 1 control was included). All of the case patients agreed to participate in the study. Six controls refused and were replaced by the next delivery. The total sample included 903 case patients and 1526 controls.

By definition, control women had achieved an intrauterine pregnancy. No women admitted for induced abortion were included in this group (in France, women requiring induced abortion are mostly referred to specialized centers unconnected with maternity centers). Some of the case patients would probably have chosen to interrupt their pregnancy if it had been normal. This differential selection may introduce a bias when studying factors linked to the decision of pregnancy termination (such as prior induced abortion). To avoid such a bias, we adopted the strategy proposed by Weiss et al.[17] and limited our study to women who were married or living with their partner as a couple and who were not using contraceptives at the time of conception (i.e., 570 case patients and 1385 controls). These were not necessarily women who wanted to become pregnant and who would not have undertaken induced abortions, but this strategy made case patients and controls comparable.

Data Collection

In each center, a trained midwife or an obstetric consultant was in charge of subjects' inclusion and data collection. During the hospitalization, case patients and controls were interviewed about sociodemographic characteristics (age, educational level, occupation), age at first intercourse, smoking habits, gynecological history (including any lower genital tract

TABLE 2—Risk of Ectopic Pregnancy Associated with Previous Induced Abortion: All Subjects

	Case Patients (n = 570), No.	(%)	Controls (n = 1385), No.	(%)	Odds Ratio[a] (95% Confidence Interval)	Adjusted Odds Ratio[b] (95% Confidence Interval)
Previous induced abortion						
No	442	(77.5)	1160	(83.8)	1.0 ...	1.0 ...
Yes	128	(22.5)	225	(16.2)	1.5 (1.1, 1.9)	1.3 (0.9, 1.8)
No. previous induced abortions						
0	442	(77.5)	1160	(83.8)	1.0 ...	1.0 ...
1	101	(17.7)	193	(13.9)	1.3 (1.0, 1.8)	1.2 (0.9, 1.8)
≥2	27	(4.7)	32	(2.3)	2.2 (1.3, 3.8)	1.4 (0.8, 2.8)
					Trend test: $P<.001$	Trend test: $P=.15$

[a]Adjusted for the maternity center.
[b]Adjusted for maternity hospital, maternal age, number of prior pregnancies, prior genital infection, prior ectopic pregnancy, current smoking, prior pelvic surgery, induced ovulation, and prior contraception.

TABLE 3—Risk of Ectopic Pregnancy Associated with Previous Induced Abortion: Women with No Previous Ectopic Pregnancy

	Case Patients (n = 471), No.	(%)	Controls (n = 1362), No.	(%)	Odds Ratio[a] (95% Confidence Interval)	Adjusted Odds Ratio[b] (95% Confidence Interval)
Previous induced abortion						
No	362	(76.9)	1145	(84.1)	1.0 ...	1.0 ...
Yes	109	(23.1)	217	(15.9)	1.6 (1.2, 2.1)	1.5 (1.0, 2.0)
No. previous induced abortions						
0	362	(76.9)	1145	(84.1)	1.0 ...	1.0 ...
1	84	(17.8)	188	(13.8)	1.4 (1.1, 1.9)	1.4 (1.0, 2.0)
≥2	25	(5.3)	29	(2.1)	2.8 (1.6, 4.9)	1.9 (1.0, 3.7)
					Trend test: $P<.001$	Trend test: $P=.02$

[a]Adjusted for the maternity center.
[b]Adjusted for maternity hospital, maternal age, number of prior pregnancies, prior genital infection, current smoking, prior pelvic surgery, induced ovulation, and prior contraception.

infection without clinical upper pelvic involvement, pelvic inflammatory disease, endometriosis, and prior contraception), reproductive history (parity, prior spontaneous or induced abortions, and prior ectopic pregnancy), history of pelvic or abdominal surgery, and conditions of the conception (contraception at the time of conception, ovulation induction). A blood sample was collected and tested for *Chlamydia trachomatis* antibodies. Sera with a titer equal to or greater than 1/64 were considered positive.

Analysis

The associations between risk factors and ectopic pregnancy were measured with odds ratios (ORs). The study design, with controls being the women admitted for delivery immediately after the case patients in the same maternity centers, was a surrogate for randomization among women admitted for delivery rather than a true matching procedure. On the other hand, this was a multicentric study. Therefore, unconditional logistic regression was used, but maternity center was included in the model as a stratification variable. Confounding factors were taken into account by standard methods of stratified analyses (Mantel–Haenszel procedure),[18] and interactions between previous induced abortion and other risk factors were systematically tested according to the usual recommendation in epidemiological studies.[19] In cases of interactions with risk factors, our general strategy was either to perform separate analyses in the factor categories or to include interaction terms in the multivariate models. In addition to the maternity center, the variables entered in the logistic regression models included the known ectopic pregnancy risk factors: prior genital infection (none, lower genital tract infection, clinical pelvic inflammatory disease, and/or *C trachomatis* seropositivity), prior ectopic pregnancy, smoking at the time of conception, previous pelvic surgery, induced ovulation, and previous contraception. Furthermore, we considered maternal age (because the probability of having experienced any investigated past event is dependent on the duration of potential exposure) and number of previous pregnancies (which constitutes a potential confounding factor because of higher numbers shown among women experiencing an ectopic pregnancy and among women with prior induced abortions).

Results

Comparisons between case patients and controls in terms of sociodemographic and medical history characteristics are shown in Table 1. The role of factors classically known as ectopic pregnancy risk factors (namely prior genital infection, smoking at the time of conception, prior ectopic pregnancy, previous pelvic surgery, and induced conception cycle) was confirmed

with our sample. Women with ectopic pregnancies were older and had a higher number of previous pregnancies, as has usually been reported.

The association between prior induced abortion and ectopic pregnancy for the sample as a whole is shown in Table 2. A higher proportion of case patients (22.5%) than controls (16.2%) experienced a previous induced abortion (OR = 1.5, 95% CI = 1.1, 1.9). Furthermore, when number of previous included abortions was considered, we observed a significant trend between the number of such abortions and ectopic pregnancy. After adjustment for potential confounders, the increased risk of ectopic pregnancy associated with previous induced abortion and the "dose–effect" relationship did not remain significant ($P = .15$).

We found a significant interaction between previous induced abortion and previous ectopic pregnancy; among women with no previous ectopic pregnancy (n = 1833), the risk of ectopic pregnancy was significantly increased for those who had one or more previous induced abortions (OR = 1.6, 95% CI = 1.2, 2.1) (Table 3). On the contrary among women who had already experienced an ectopic pregnancy (n = 122), the risk of recurrence did not differ significantly whether they had a previous induced abortion or not (OR = 0.5, 95% CI = 0.2, 1.4). The interaction (i.e., the difference between these two odds ratios) was significant ($P = .03$).

The multivariate analysis involved women with no previous ectopic pregnancy; a logistic regression model included the same variables as in the previous analysis (except prior ectopic pregnancy). Results (Table 3) showed a persistent significantly increased risk of ectopic pregnancy among women who had a previous induced abortion (OR = 1.5, 95% CI = 1.0, 2.0). Moreover, there was a significant trend ($P = .02$) between the number of previous induced abortions and the risk of ectopic pregnancy, with a higher risk in women with two or more prior induced abortions.

Discussion

Our study provides an argument for the existence of an association between previous induced abortion and ectopic pregnancy. Its most original result is that prior induced abortion is associated with an increased risk of subsequent ectopic pregnancy only among women who have not experienced such an abnormal implantation. The absence of association between previous induced abortion and risk of ectopic pregnancy among women who had a previous ectopic pregnancy is difficult to interpret because, in our study, the chronological order of different previous reproductive events was unknown. We therefore decided to conduct the final multivariate analysis only among women with no previous ectopic pregnancy. We did not exclude women without a prior pregnancy because, in the present analyses, they had to be considered as nonexposed rather than noninformative. We did not consider induced abortion as a risk marker and aimed to assess the effect of the act of induced abortion itself on the risk of subsequent ectopic pregnancy. However, we adjusted for the number of previous pregnancies, and we verified that the results for the multiparous women were quantitatively very similar to those for the entire sample.

Selection bias was possible but probably limited. Case patients and controls had similar educational levels and adjustments were made for maternity center. Furthermore, in France, the care pathways are similar for these 2 groups: women with possible ectopic pregnancies are generally referred to the nearest maternity hospital, and most women with an uncomplicated pregnancy deliver in a maternity center close to their residence. As already mentioned, the analysis was conducted only among women who were planning to complete their pregnancy so as to avoid the consequences of the absence of controls undergoing induced abortions.

The main source of bias involved ascertainment of previous induced abortions, which was based on subjects' self-reports. Underreporting was possible (because of poor judgment commonly associated with this event, which women may be liable not to declare). In France, the evaluated number of induced abortions for the year 1988 ranged from 22 per 100 births[20] to 30 per 100 births.[21] Considering the number of induced abortions for each woman, we noted a slightly lower ratio in our control sample: 20 declared induced abortions per 100 births. Yet a slight underrepresentation of this event was to be expected according to the initial selection of the women (women who were planning to complete their pregnancy). Similar results were found by Daling et al. in the United States.[12] Moreover, a misclassification bias could explain the observed relationship only if it was differential and concerned mainly controls but not case patients. Such a differential bias was found by Holt et al.[14] but in the reverse direction: 2% of controls failed to declare induced abortions, whereas 4% of case patients did so. Although a differential misclassification bias cannot be excluded, we believe it unlikely that either its magnitude or its direction could explain our results. Finally, we cannot exclude the existence of confounding effects of unidentified risk factors, but the diversity of the investigated exposures made them improbable.

No other study has shown a significant association between previous induced abortion and risk of ectopic pregnancy since the 1972 Greek study of Panayotou,[10] who found a very strong link between these two events (estimated OR = 10) probably explained by the high incidence of infectious complications at a time when induced abortion was illegal. The apparent discordance of our results with those of most previous studies may be primarily the consequence of the high number of subjects (sufficient to detect an odds ratio of 1.5 with a statistical power of 80%). Most of the other studies did not have enough power to detect odds ratios of the order of 1.5.[12,14,15] Only Levin et al.,[11] working with a relatively small sample found high (but minimally significant) odds ratios, but their control group was composed of women giving birth, and there was no selection according to the initial desire for pregnancy. Thus, it cannot be ruled out that their results were the consequence of a selection bias, as explained earlier. When the number of subjects has been sufficient, there has been no consideration of an interaction between previous induced abortion and previous ectopic pregnancy. Burkman et al.,[13] who studied a large number of women did not find an association between previous induced abortion and ectopic pregnancy. However, their analysis adjusted for previous ectopic pregnancy without any term of interaction, which may have masked an association present only in women with no previous ectopic pregnancies. It is noteworthy that, in our study, no significant association was observed (Table 2) when this interaction was not taken into account. Moreover, Daling et al.,[12] studying a sample of women with no prior history of ectopic pregnancy, found odds ratios very similar to those described here (adjusted odds ratios of 1.4 for one previous induced abortion and 1.8 for two or more previous induced abortions). The number of subjects included in their study may have been insufficient, however, to reach the level of statistical significance.

The induced abortions described in the present study were probably all surgical ones (because the medical method for induced abortion has been used in general only since the early 1990s). The association observed between induced abortion and risk of subsequent ectopic pregnancy could be the consequence of uterine injuries consec-

utive to this procedure, either inflammatory lesions or asymptomatic postsurgical ascending infections (symptomatic infections were considered in our analysis). Recent studies (e.g., Larson et al.[22]) have pointed out the necessity of better defining the women undergoing abortion who are at risk of pelvic infections and who should receive prophylactic treatment with antibiotics. Our results constitute a supplementary argument for doing so.

In conclusion, this study, which analyzed a large sample of women, provides an argument for the existence of a significant association between induced abortion and subsequent ectopic pregnancy in France. This predisposition to ectopic pregnancy after induced abortion, if confirmed, constitutes a worrisome issue (especially for women with two or more induced abortions), since induced abortion is a relatively frequent event. Further investigations are needed to understand better the physiopathological mechanisms involved and ways in which to counteract them. In particular, more detailed analyses differentiating medical and surgical methods for induced abortion could be of great interest. Moreover, studies should be planned to investigate the reproductive outcomes of women who have experienced induced abortions. □

References

1. Jehle D, Krause R, Braen R. Ectopic pregnancy. *Emerg Med Clin North Am.* 1994;12: 55–71.
2. Atrash HK, Hughes JM, Hogue CJR. Ectopic pregnancy in the United States, CDC surveillance summaries. *MMWR Morb Mortal Wkly Rep.* 1986;35:29–37.
3. Chow WH, Daling JR, Cates W, Greenberg RS. Epidemiology of ectopic pregnancy. *Epidemiol Rev.* 1987;9:70–94.
4. Coste J, Job-Spira N, Aublet-Cuvelier B, et al. Incidence of ectopic pregnancy. First results of a population-based register in France. *Hum Reprod.* 1994;9:742–745.
5. Centers for Disease Control. Ectopic pregnancy—United States, 1988–1989. *MMWR Morb Mortal Wkly Rep.* 1992;41:591–594.
6. Coste J, Job-Spira N, Fernandez H, Papiernik E, Spira A. Risk factors for ectopic pregnancy: a case control study in France, with special focus on infectious factors. *Am J Epidemiol.* 1991;133:839–849.
7. Weström L. Influence of sexually transmitted diseases on fertility and ectopic pregnancy. *Acta Eur Fertil.* 1985;16:21–24.
8. Marchbanks PA, Annegers JF, Coulam CB, Strathy JH, Kurland LT. Risk factors for ectopic pregnancy. A population-based study. *JAMA.* 1988;259:1823–1827.
9. Job-Spira N, Collet P, Coste J, Brémond A, Laumon B. Facteurs de risque de la grossesse extra-utérine. Résultats d'une enquête cas-témoins dans la région Rhône-Alpes. *Contracept Fertil Sex.* 1993;21:307–312.
10. Panayotou P, Kaskarelis D, Miettinen I, et al. Induced abortion and ectopic pregnancy. *Am J Obstet Gynecol.* 1972;114:507–510.
11. Levin AA, Schoenbaum SC, Stubblefield PG. Ectopic pregnancy and prior induced abortion. *Am J Public Health.* 1982;72:253–256.
12. Daling JR, Chow WH, Weiss NS. Ectopic pregnancy in relation to previous induced abortion. *JAMA.* 1985;253:1005–1008.
13. Burkman R, Mason K, Gold E. Ectopic pregnancy and prior induced abortion. *Contraception.* 1988;37:21–27.
14. Holt VL, Daling JR, Voigt LF, et al. Induced abortion and the risk of subsequent ectopic pregnancy. *Am J Public Health.* 1989;79: 1234–1238.
15. Kalandidi A, Doulgerakis M, Tzonou A, Hsieh C, Aravandinos D, Trichopoulos D. Induced abortions, contraceptive practices, tobacco smoking as risk for ectopic pregnancy in Athens, Greece. *Br J Obstet Gynecol.* 1991; 98:207–213.
16. Coste J, Laumon B, Brémond A, et al. Sexually transmitted diseases as major causes of ectopic pregnancy: results from a large case-control study in France. *Fertil Steril.* 1994; 62:289–295.
17. Weiss NS, Daling JR, Chow WH. Control definition in case-control studies of ectopic pregnancy. *Am J Public Health.* 1985;75:67–68.
18. Breslow NE, Day NE. *Statistical Methods in Cancer Research. Volume 1: The Analysis of Case-Control Studies.* Lyon, France: International Agency for Research on Cancer; 1980. IARC scientific publication 32.
19. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic Research. Principles and Quantitative Methods.* Belmont, Calif: Lifetime Learning Publications; 1982.
20. *Statistiques de l'Avortement en France-Annuaire 1988.* Paris, France: Editions INED; 1993.
21. Blayo C. L'évolution du recours à l'avortement en France depuis 1976. *Population.* 1995;50:779–810.
22. Larsson PG, Platz-Christensen JJ, Thejls H, Forsum U, Påhlson C. Incidence of pelvic inflammatory disease after first-trimester legal abortion in women with bacterial vaginosis after treatment with metronidazole: a double-blind randomized study. *Am J Obstet Gynecol.* 1992;166:100–103.